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— THE 71st CALEB FISKE PRIZE ESSAY —
THE PRESENT STATUS OF ADRENO-CORTICAL HORMONE THERAPY, ITS USES AND LIMITATIONS*

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INTRODUCTION

IN THE THREE YEARS that ACTH and cortisone have been in clinical use there has been a remarkable change in attitude toward them. Initially they commanded little enthusiasm. Two pioneers in the field, Long and Kendall, both pessimistically predicted the compounds would have virtually no clinical usefulness.[1, 2] By contrast enthusiasm now has risen so high that when a disorder not previously treated with ACTH or cortisone is found, its treatment merits publication. Only the shortage and cost of these hormones have prevented their widespread promiscuous use in a manner reminiscent of vitamins and antibiotics. Not only do these hormones ameliorate a wide spectrum of inflammatory, allergic and fibroblastic disorders, but they may have analgesic, antipyretic and euphoric effects. However, as dramatic as these effects are, it appears on calm appraisal that ACTH and cortisone also have many undesirable and dangerous physiologic actions. Further, there is no evidence that either hormone actually cures any disorder. These shortcomings and their management will be stressed in the second part of this review.

The intelligent clinical use of ACTH and cortisone requires some understanding of pituitary-adrenal mechanisms and the chemistry and physiology of the respective hormones.

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Pituitary-Adrenal Physiology

The anterior pituitary, without necessary connection with the hypothalamus or nervous system, can respond to two separate stimuli—called "autonomic" and "metabolic" by Long.[3] Autonomic pathways cause secretion of adrenalin with prompt direct stimulation of pituitary ACTH release. Metabolic control is mediated by a fall in blood steroid level which stimulates ACTH release. Both methods of stimulation may result from stress which causes adrenalin secretion and increased adrenal steroid utilization. The only known way of stimulating the adrenal cortex is with ACTH, a potent protein or polypeptide not known to have any other action. There are at least 28 different adrenal steroids, many of which may be breakdown products of body metabolism or artifacts of chemical isolation and identification. There is evidence to suggest that compound F is the principal steroid made by the adrenal. (Fig. 1)

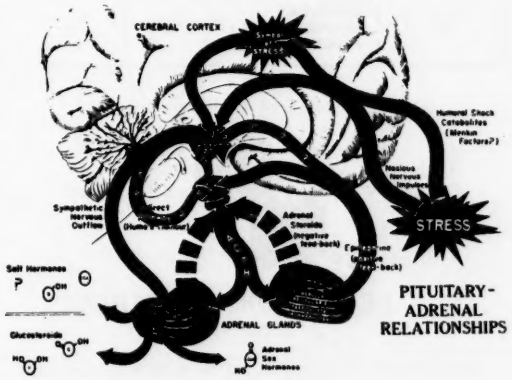

Figure I

The usual classification into (1) adrenal sex steroids (protein anabolic), (2) adrenal sugar steroids (protein catabolic), and (3) adrenal salt steroids (like desoxycorticosterone, which has not been isolated in the human being) may be more a convenience than a reality. However, it is useful to think of three separate effects. First, the adrenal

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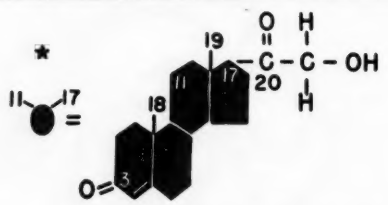
sex steroids cause acne, hirsutism, baldness, and occasionally direct genital effects. Pituitary gonadotropins may be suppressed causing gonadal atrophy with loss of libido and amenorrhea. Secondly, the adrenal sugar steroids cause an impaired glucose utilization so that tissues appear to require a higher blood sugar level in order to oxidize glucose in normal amounts. The rise in blood sugar is derived by gluconeogenesis from protein and probably fat.[4] The consumption of protein to make sugar causes wasting of the body muscle mass, impairs wound healing, inhibits fibroblast and lymphocyte production, phagocytosis, causes eosinopenia, stops growth, and in ways unknown is responsible for the suppression of inflammatory processes. Thirdly, the adrenal salt steroids cause a diuresis of potassium, which may result in potassium deficiency, and a retention of salt and water leading to edema, congestive failure, and possibly hypertension. Figure II summarizes these actions and presents a simple method of remembering the different steroid molecules by using DOCA as a nucleus.

CONFIGURATION	NAME	METABOLIC EFFECT		ANTI-INFLAMMATORY EFFECT
		SALT	SUGAR	
	DESOXY-CORTICOSTERONE	++++	0	0
O	COMPOUND A	++	++	0
HO	COMPOUND B	++	+++	0 ?
OH	COMPOUND S	++++	0	0
O OH	COMPOUND E (CORTISONE)	+	++++	++++
HO OH	COMPOUND F (HYDRO CORTISONE)	++	+++++	++++
?	AMORPHOUS FRACTION	+?	+?	0



DESOXYCORTICOSTERONE

Figure II

Compound E or cortisone acetate is a chemically pure, synthetic steroid that does not need biological standardization. It is a highly insoluble suspension of crystals given by intramuscular injection. The maximum effect of a single 100 mg. injection does not appear for 24 hours.[5] Thus it may be likened to protamine zinc insulin in that it produces a cumulative response during the first five or six days of injection. That adrenal steroids are effective orally has been known since 1931,[6] and a 25 mg. tablet of cortisone acetate has been commercially available for over a year. Cortisone given orally simulates the result of intravenous injection with a more prompt and short-lived effect than if given by intramuscular injection.[7, 8, 9, 10, 5] The peak effect occurs in 4-6 hours with a duration of 8-12 hours after a 50 mg. dose.[5] It is not known which route will become most widely used since the intramuscular injection gives a more constant blood level and the oral preparation must be administered every 6 hours, may cause flatulence, and is more expensive. However, convenience of administration and rapidity of action insure its widespread use.

Dosage should begin high enough to attain optimal amelioration of the disease. This may require 400 mg. a day in single or multiple intramuscular injections or two to four 25 mg. tablets orally every six hours. The dosage may then be reduced gradually to the usual maintenance of a total 50-100 mg. per day. When it is desired to stop treatment it is wise to taper off over a minimum of ten days, reducing the daily dose by approximately ten per cent each day. During the last three days of therapy some investigators advise giving 10 mg. of ACTH-gel every day to help restore the atrophic adrenal glands.

ACTH is a biologically standardized protein extracted from animal pituitaries. It is highly soluble in water and may be injected intravenously as well as subcutaneously. Its effect is prompt and short lived requiring injections every six hours unless the respository ACTH-gel is used. This may be given but once a day; however, it is only 70% as effective as the divided dose administration of regular ACTH. Intravenously the hormone is effective in small amounts, but continuous infusion over many hours is necessary. A liter of 5% glucose and water containing 20 mg. of ACTH may be allowed to drip through a long No. 26 intravenous needle over an eight-hour period.[11, 12] This is the least expensive method of administering adrenal hormone therapy but it is also the most cumbersome and inconvenient. Regular subcutaneous injection usually requires 40-120 mg. per day in divided doses but as much as 300 mg. per day is not unusual. ACTH is not effective orally or locally. Table I summarizes a comparison between ACTH and cortisone.

PART I.

The Uses of Adreno-Cortical Hormone Therapy

In reviewing the disorders treated by ACTH and cortisone it may be desirable to classify them as follows (See Table II). First are those in which the hormone is an actual substitution for a glucosteroid deficiency. That this is a rare situation needs emphasis. All other uses of these hormones are empirical and based upon the unphysiologic effects of excessive amounts of the hormone within the

TABLE I

Comparison of ACTH and Cortisone

ACTH	*CORTISONE*
1. A protein extract	1. A pure synthetic steroid
2. Biological standardization	2. Gravimetric standardization
3. Allergic reactions in 3%	3. Not antigenic
4. Causes adrenal hypertrophy	4. Causes adrenal atrophy
5. Danger of overstimulating the adrenal in stress?	5. Protects the adrenal in stress
6. Stimulates the secretion of all three adrenal steroid groups	6. Replaces only glucosteroids Depresses other steroid groups
7. Contraindicated in adrenogenital syndrome	7. Indicated in adrenogenital syndrome
8. Sodium-water retention marked	8. Sodium-water retention less marked
9. Hypertension common	9. Hypertension uncommon
10. No effect if adrenals unresponsive	10. Effective if adrenals unresponsive
11. No effect locally	11. Effective locally
12. No effect orally	12. Effective orally
13. 2-3 times as effective as cortisone by weight	13. 1/4th as effective as ACTH by weight
14. I.V. economical; cumbersome	14. I.V. experimental
15. Repository gel 70% effective over 24 hrs.	15. Crystal suspension 100% effective over 24 hrs.
16. 1 Gm costs $93	16. 1 Gm costs $20

body. Second are inflammatory processes which cannot be controlled by specific therapy. Third are toxic states for which there is no effective antitoxin. Fourth are immunologically undesirable conditions such as allergy. Fifth are fibroblastic and other cellular growth reactions which must be inhibited. Sixth are metabolic defects for which these hormones can compensate. Seventh are several diseases not yet known to belong to any of the previous six groups.

TABLE II

Uses of Adreno-Cortical Hormone Therapy

I. Glucosteroid Deficiency States
1. Panhypopituitarism
2. Addison's disease
3. Acute adrenal failure (Waterhouse-Friderichsen's syndrome)
4. Functional adrenocortical insufficiency
5. Adrenogenital syndrome, esp. macrogenitosomia praecox

II. Inflammatory Conditions
1. Inflammatory conditions of the eye
   a. Vernal conjunctivitis
   b. Iritis
   c. Keratitis
   d. Chorioretinitis
   e. Iridocyclitis
   f. Sympathetic ophthalmia
   g. Inflammatory exophthalmos
   h. Optic neuritis
2. Inflammatory conditions of the joints
   a. Rheumatoid arthritis
   b. Psoriatic arthritis
   c. Rheumatic fever
   d. Gout
   e. Reiter's syndrome
   f. Allergic arthritis
   g. Non-suppurative arthritis
   h. Suppurative arthritis
   i. Other collagen diseases
3. Inflammatory conditions of the cardiovascular system
   a. Rheumatic myocarditis
   b. Polyarteritis nodosa
   c. Cranial arteritis
   d. Thromboangiitis obliterans
   e. Thrombophlebitis
   f. Phlebitis migrans
4. Inflammatory conditions of the intestinal tract
   a. Ulcerative colitis
   b. Regional enteritis
   c. Typhoid enteritis
5. Inflammatory conditions of the skin
   a. Exfoliative dermatitis
   b. Sumac dermatitis
   c. Discoid lupus
   d. Contact dermatitis
   e. Dermatomyositis
   f. Atopic eczema
   g. Psoriasis
   h. Pemphigus
6. Other inflammatory conditions
   a. Lupus erythematosis
   b. Dermatomyositis
   c. Acute viral hepatitis
   d. Acute glomerulonephritis

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e. Thyroiditis
f. Pancreatitis
g. Hunner's ulcer
h. Osteitis pubis

III. Toxic States
1. Known toxins
a. Tetanus
b. Diphtheria
c. Snake bite
d. Black widow bite
2. Severe infections
a. Peritonitis
b. Typhoid fever
c. Meningococcemia
d. Tuberculosis
3. Severe burns

IV. Immunologic Disorders
1. Allergic reactions
a. Drug eruptions
b. Erythema multiforme
c. Stevens-Johnson's syndrome
d. Anaphylactoid purpura
e. Contact dermatitis
f. Angioneurotic edema
g. Ide reactions
h. Loeffler's syndrome
i. Vasomotor rhinitis
2. Thrombocytopenic purpura
3. Acquired hemolytic anemia
4. Hyperimmune reactions

V. Disorders of Cellular Growth
1. Undesirable fibroblastic reactions
a. Beryllosis
b. Bissinosis
c. Chronic pulmonary fibrosis
d. Scleroderma
e. Burn granulations
f. Cirrhosis
g. Polyposis
h. Sarcoidosis
i. Eosinophilic xanthomatous granulomata
2. Leukemia
3. Hodgkin's disease
4. Lymphosarcoma
5. Multiple myeloma
6. Thymoma—myasthenia gravis

VI. Metabolic Disorders
1. Idiopathic hypoglycemia
2. Nephrosis
3. Nontropical sprue

VII. Miscellaneous Disorders
1. Arteriosclerosis obliterans
2. Raynaud's disease
3. Tabes dorsalis
4. Multiple sclerosis
5. Alcoholism
6. Drug addiction
7. Baldness
8. Myocardial infarction

The merit of this classification lies in its prompting one to consider using ACTH or cortisone in treating other wholly unrelated conditions which may share the feature of toxicity, inflammation, antibody mechanism, fibroblastic proliferation, etc.

At the present time it is impossible to assess the value of administering ACTH or cortisone in many of the disease states listed in Table II because of the small number of patients reported and the variation in intensity of symptoms inherent in the disease. For example, partial spontaneous remissions are surprisingly common in most of these disorders, even the malignant conditions, lymphomas, leukemias, and multiple myeloma.

For these reasons, indications for the use of ACTH or cortisone should still be viewed conservatively.

I. GLUCOSTEROID DEFICIENCY STATES

There are five conditions manifesting a glucosteroid deficiency: panhypopituitarism, Addison's disease, acute adrenal failure (such as Waterhouse-Friderichsen's syndrome), "functional adrenocortical insufficiency," and certain cases of adrenogenital syndrome, especially macrogenitosomia praecox which frequently results in death from adrenal insufficiency.[13, 14]

ACTH therapy is rational only in the first, and even here for long range maintenance it is less practical and more expensive than oral cortisone. Cortisone may be lifesaving in all five conditions, using remarkably small doses of only 10-30 mg. per day. There is no danger of undesirable effects when substitution therapy is being used.

Waterhouse-Friderichsen's syndrome requires special comment. This fatal hemorrhagic necrosis of the adrenal occurs in conditions of extreme stress with maximal ACTH release combined with a purpuric or bleeding tendency. Properly the term refers only to the hemorrhagic necrosis associated with fulminating meningococcemia, but a clinically and pathologically indistinguishable picture results in some instances of severe burns, septicemia, fulminating malaria and toxemia of pregnancy.[15] It would seem logical to anticipate that the use of ACTH in such a situation might further damage the already overstimulated adrenal gland.[16, 17] This possibility has not been evaluated experimentally. However, one careful study[18] demonstrated that monkeys with fulminating malaria or diphtheria die with hemorrhagic necrosis of the adrenals. The administration of lipo-adrenal extract alone completely prevented adrenal necrosis, allowing significant prolongation of life, even though the infection

was accelerated. It appears probable this hormonal prolongation of life might allow simultaneous chemotherapy time enough to cure.

Although ACTH as well as cortisone has been used in severe burns there are no reports of hemorrhagic adrenal necrosis at autopsy, so this fear of ACTH remains theoretical.

II. INFLAMMATORY CONDITIONS

Conditions manifesting predominantly inflammatory reactions make up the largest group of disorders responding to ACTH or cortisone. How these hormones make cells unresponsive to irritants is not known, but the site of action may well be intracellular. If specific treatment is possible, this is desirable since ACTH and cortisone do not eradicate the irritant itself.

1. Inflammatory Conditions of the Eye

Inflammatory conditions of the eye that have been treated with ACTH or cortisone include vernal conjunctivitis, iritis, keratitis, optic neuritis, chorioretinitis, and iridocyclitis, associated with any underlying process such as rheumatoid arthritis, tuberculosis, or sarcoidosis. 50%-90% of patients have shown improvement.[19, 20, 21, 22, 23] Sympathetic ophthalmia (which may have an immunologic basis), and some cases of inflammatory exophthalmos may also be benefited. Cortisone may be administered systemically or locally. Cortisone eye drops may be made by diluting the commercial suspension five times with sterile saline. Vision is undoubtedly salvaged in many instances.

Stopping therapy requires a slow tapering off with careful observation since some patients will relapse and become worse than before treatment. A previously unilateral iritis may become bilateral when treatment is stopped.[24]

2. Inflammatory Conditions of the Joints

Rheumatoid arthritis, psoriatic arthritis, gout, Reiter's syndrome, rheumatic fever, allergic arthritis, non-suppurative arthritis associated with leukemia, tuberculosis, typhoid or other infections, and other collagen diseases appear to be completely or markedly suppressed if the dosage of hormone is high enough. Unfortunately if the underlying disease process remains, the arthritis tends to return when therapy is stopped. Suppurative arthritis, especially gonococcal, brucellar or tuberculous, responds symptomatically but the underlying bacterial growth is unchanged and must be treated by the usual methods.

Clinically, the first non-endocrine disorder to receive adrenal hormone therapy,[25] rheumatoid arthritis, has been treated in at least 940 reported cases. Although the initial response is usually excellent with relief of pain, reduction in stiffness, and suppression of inflammation, the degree of improvement varies with the severity of the disease. In a series of 107 patients, only 18% of the advanced cases had benefit, whereas 50% of the moderately advanced and 73% of the early cases had good responses.[26] Whether this clinical improvement has anything to do with the reported[27] deficiency of adrenal steroids in rheumatoid arthritis is only a source of speculation, but it seems doubtful. One long term study including synovial biopsy[28] concludes, "ACTH altered promptly and dramatically all the manifestations of disease activity but the reversal was not complete (after 130 days) and the underlying disease process was not eradicated." This impression is borne out by the rarity of sustained remission after stopping treatment. Probably no more than 5% fall into this group. Therapy should not be interrupted, but decreased gradually over many months. Permanent maintenance may be necessary. The economic features of this possibility should be explored before attempting treatment.

3. Inflammatory Conditions of the Cardiovascular System

Since the first optimistic report[29] of the ability of ACTH to suppress all clinical signs of activity in 10 patients with rheumatic fever, there have been many confirmatory studies. In 131 patients[30, 31, 32, 33] there has been prompt improvement in the majority, although a few appear to become worse. The hope that one might prevent the serious sequelae of valvular damage is widely held but little evidence is available. One preliminary report[34] is pessimistic because of 20 treated patients with acute rheumatic fever, the four with myocarditis were found to have valvular disease seven months later. An autopsy report[35] of an ACTH and cortisone treated patient "failed to reveal any deviation from the changes usually seen in a non-cortisone treated patient with rheumatic carditis." There is reason to believe that the duration of the illness is not altered by ACTH. When therapy is stopped, the prompt reappearance of symptoms suggests an unmasking of the original process, rather than a recurrence of rheumatic fever. This reappearance may be more severe than the initial illness.[32] Thus treatment should be given over a period consistent with the natural history of the disease (4-10 weeks) and then very slowly tapered off, being ready to restart full doses at the first evidence of activity. Therapy over this long a period runs the risk of undesirable effects, particularly congestive failure in patients with damaged hearts. Evaluation of the effectiveness of ACTH or cortisone is difficult since the arthritis, malaise, fever, sedimentation rate, and white blood count are directly altered by the hormones.[36, 37] Probably the only valid criterion is a prolonged follow-up analysis for valvular damage. Other types of myocarditis, such as Feidler's myocarditis, might also re-

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spond but treatment would be hazardous because of the danger of precipitating congestive failure.

Polyarteritis nodosa has been treated in at least 16 cases.[38, 39, 2, 40, 41, 42, 43, 44] The inflammatory features of the disease show impressive initial improvement, but death usually ensues in spite of therapy. One autopsy report[40] suggested that infarction in the major viscera resulted from therapy because of too rapid healing. Malignant hypertension may also occur.[45]

Cranial arteritis was promptly relieved in two patients.[42] Since this is usually a self-limiting disease the outcome should be favorable. There are also reports of good results in thromboangiitis obliterans,[38], phlebitis migrans,[38] and thrombophlebitis,[46] although others claim ACTH may produce thrombophlebitis (See Part II below).

4. Inflammatory Conditions of the Intestinal Tract

Ulcerative colitis has been treated in 99 patients,[47, 38, 48, 49, 50, 51] One series of 40[50] reports 27 good results, 7 moderate, 2 slight, no change in 4 and a sustained remission in 15. Complications included suicide, fatal perforation, pneumonia, furunculosis, buttocks abscess and urticaria. ACTH usually produced an impressive increase in appetite and sense of well-being. This was followed within a few days by disappearance of fever, fall in sedimentation rate, loss of toxicity, diminution in the number of bowel movements, fall in fecal lysozyme, and later by an increase in hematocrit, plasma proteins and body weight. Of course no remission occurred in patients with diffuse cicatrization and extensive fibrosis. The optimal period of therapy is probably three to six weeks. It is well to emphasize that relapses occurred in most patients several months after stopping ACTH. This fact combined with "the persistence of occult blood in the stools associated with some residual evidence of activity on sigmoidoscopic examination emphasizes the fact that ACTH does not cure the disease."[47]

The response of typhoid enteritis to cortisone and chemotherapy is more prompt than to chemotherapy alone.[52, 53]

Regional enteritis responds in a manner similar to ulcerative colitis according to treatment of 14 cases.[47, 44, 54] Benefit is more likely if the patient is treated early in an acute phase.

5. Inflammatory Conditions of the Skin

As with the previous conditions, inflammation of the skin, no matter what its cause, may be strikingly benefited by ACTH and cortisone. Eczemas, exfoliative dermatitis, sumac dermatitis, discoid lupus, contact dermatitis, dermatitis herpetiformis, turpentine abscess, mycosis fungoides, dermatomyositis, pemphigus,[55, 56, 57, 58] and psoriasis[56] are reported to be ameliorated.[59, 58, 56] Chronic rashes are more variable in their response. If the cause is still present after stopping therapy, relapse is prompt and may leave the patient with a more severe form of his disease than he had before treatment. Atopic eczema, psoriasis and discoid lupus, the worst offenders in this regard, may be contraindications for ACTH therapy.

6. Other Inflammatory Conditions

Lupus erythematosis has been treated with ACTH or cortisone in 86 cases.[61, 62, 63, 64, 65, 38, 2, 66, 67, 68] The response is variable. The L.E. cell test may be suppressed, but there have been no complete clinical remissions. The renal lesions are especially persistent—in only one reported patient, treated continuously for 73 days, has there been a clearing of the urine.[61]

Dermatomyositis also responds in a variable manner. When it is acute with a marked inflammatory component, the response is most striking. Discontinuing therapy is usually followed by a prompt recurrence of the inflammation, but patients may return to work on maintenance therapy. Testosterone in addition to cortisone is recommended. There is certainly no other therapy so likely to be helpful. Of 8 adults and 4 children, 1 adult and 3 children are in partial remission.[2, 56]

Acute viral hepatitis has been treated in 23 cases [75, 71, 72] with marked symptomatic improvement.

Acute glomerulonephritis has been treated with inconclusive results in 12 patients.[73, 74, 38, 75] One patient appeared to be harmed rather than helped.[75] There is even reason to believe that ACTH may predispose to an attack of acute glomerulonephritis. [76, 55] Certainly in patients on therapy for other reasons it failed to prevent the incidental occurrence of acute nephritis.

Thyroiditis is reported to have responded promptly in 5 patients,[2, 77] suggesting the desirability of further trial.

Acute pancreatitis may have been benefited in two patients.[46] Adrenal steroids cause a fall in serum amylase[79] by unknown means so this guide to response in treating pancreatitis is not reliable.

Hunner's ulcer (intersitial cystitis) responded in 4 patients[80] but relapsed in all when therapy was withdrawn.

Osteitis pubis showed improvement in three cases.[81]

III. TOXIC STATES

Although the term toxicity lacks precision, it has wide usage. It can properly be applied to the known toxins, several of which may be neutralized by ACTH alone or in conjunction with the specific antitoxin. It has been mentioned[18] that monkeys dying of diphtheria infection may have their lives prolonged with lipo-adrenal extract, but there are no clinical reports.

One patient with tetanus of severe degree made a remarkable response to ACTH, then relapsed and died.[2] However, this outcome may have been due to small adrenals that were unable "to continue to respond to ACTH." Since tetanus toxin is fixed within the cell, inaccessible to antitoxin, it was believed the benefit in this case might argue that the hormone exerted its effect directly within the cell.

Preliminary reports of patients toxic from copperhead snake-bite and black widow spider-bite state they became well with only one or two injections of ACTH.[82] No confirmation of this report has appeared.

The so-called toxic state associated with severe infections is of importance since the patient often dies from toxicity before the proper antibiotic can cure the infection. Kinsell[2] makes an appeal for the use of ACTH in peritonitis which still takes a high toll in spite of antibiotics.

Equally dramatic is Finland's[83] now famous report on the effect of ACTH in completely suppressing toxicity in a patient with lobar pneumonia, even though his blood cultures became positive and the pneumonia spread by x-ray. The toxicity of typhoid fever responds promptly to cortisone as stated above. Certain types of tuberculosis may be indications for combined antibiotic and cortisone therapy.[2]

It is essential to emphasize the dangers of such combined therapy since signs of complications are suppressed. In no infection should cortisone be used without the appropriate antibiotic and vigilance for development of complications.

The toxicity of burns is promptly suppressed permitting patients to survive extensive burns that were previously considered to be invariably fatal. The first report[84] was so striking it was received with scepticism but there have been confirmatory reports.[85, 86] It is now difficult to explain why some patients free of toxicity lapse into coma and die.[87]

IV. CONDITIONS WITH UNDESIRABLE IMMUNOLOGICAL MECHANISMS

For several years it was thought that adrenal steroids caused an increased release of antibodies.[88] Subsequently these findings could not be confirmed.[89, 90, 91] It is now conceded that not only are immune mechanisms not enhanced, but their effectiveness is somehow blocked. In the presence of cortisone an antigen can stimulate the normal production of antibodies; antigen and antibody can react with each other with consumption of complement, but the resulting complex is neutralized.[92] The clinical effect is the same as if antibody production had been suppressed in the first place.

The most striking members of this group are the allergic (hypersensitivity) diseases. Based upon reports of 257 patients with asthma it may be said that most respond temporarily during treatment, but the relapse rate is high upon stopping therapy.[93, 94, 95, 96, 97] Drug eruptions,[98] erythema multiforme,[99] Stevens-Johnson's syndrome, anaphylactoid purpura,[100] contact dermatitis, angioneurotic edema, ide reactions, Loeffler's syndrome,[101] and vasomotor rhinitis may all be indications for use of ACTH or cortisone.[98, 102, 38, 56]

Acquired hemolytic anemia mediated by antibody mechanisms may respond promptly to therapy.[103, 38, 104, 105] Cooley's anemia also may respond.[106] The rapid rise in hematocrit simulates a marrow stimulating effect. A direct marrow stimulating effect of ACTH and cortisone has not been demonstrated although alleged to occur experimentally.[60, 107]

Idiopathic thrombocytopenic purpura, which has been demonstrated by Evans[108] to be due to an antiplatelet antibody, responds dramatically to therapy in some instances.[109] This is probably not a direct stimulation of bone marrow production of platelets by ACTH. Failures[38] have also been reported.

In both acquired hemolytic anemia and primary thrombocytopenic purpura the use of these hormones may be lifesaving by producing sufficient improvement to permit splenectomy. They also provide new avenues for investigation into the basic mechanisms of these diseases.

Dangerous hyper-immune reactions, such as the lepra reaction[110] may be suppressed by ACTH. The tuberculin skin test may be reversed in patients receiving cortisone.[111, 112]

Since the harmful effects of antibodies are blocked by these hormones one wonders whether the useful immune mechanisms are not also blocked. That this may be the case is suggested by the frequent occurrence and rapid spread of infections during treatment (See Part II).

V. DISORDERS OF CELLULAR GROWTH

Several disorders involving undesirable fibroblastic growth are reported to be benefited by ACTH or cortisone therapy.

Chronic pulmonary beryllium granulomatosis (which may be an allergic disease) has been treated with a striking decrease in dyspnea, cyanosis, and disability.[113, 114, 115] Maintenance therapy is usually necessary. Silicosis[113] and pulmonary bissinosis[116] have also been reported to respond, but less dramatically. In five patients with chronic pulmonary fibrosis and emphysema 2 responded, 2 were made worse and 1 showed no change.[117]

Scleroderma has been treated with ACTH or cortisone in 14 patients with temporary slight improvement.[118, 38, 60, 120, 121] The chronic extensive nature of the fibroblastic reaction suggests that therapy must be continued indefinitely with the hope that progression might be halted, but with little expectation that fibrous tissue already formed would be reabsorbed.

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Cirrhosis of the liver has been studied on ACTH or cortisone treatment in 27 cases with variable results.[122, 123, 124, 125, 126] The largest reported experience[126] concludes, "No significant benefit was seen in patients with Laennec's cirrhosis. The complications of ACTH therapy in patients with hepatic cirrhosis are serious and constitute a contraindication to its regular use in this condition."

Sarcoidosis has been treated in 22 cases.[61, 127, 128, 117, 129, 130] The consensus is that significant improvement in pulmonary, cutaneous, lacrimal, parotid and lymph-node lesions occurred in the majority. The Kveim test became negative. Osseous and genitourinary tuberculosis developed as a complication in one patient suggesting that all treatment of sarcoid should be accompanied by streptomycin.

Hand-Schüller-Christian syndrome (eosiniphilic xanthomatous granuloma of Thannhauser) with its marked fibroblastic tendency responded to cortisone in an equivocal manner in a single case.[131]

Other disorders of cellular growth which may in some instances show response to ACTH or cortisone include acute lymphatic and myelogenous leukemia, Hodgkin's disease, lymphosarcoma, multiple myeloma and thymoma with myasthenia gravis.

Two hundred and twenty-five patients with acute leukemia have received a trial of ACTH or cortisone.[132, 133, 38, 134, 135, 136] Remissions are noted in about half and have been reported to last as long as 64 weeks with a mean of 15 weeks.[136] Contrariwise the course of acute myelogenous[136] and monocytic[134, 38] leukemia may be accelerated. Complications, especially psychoses[134, 136] are unfortunately frequent.

Chronic myelogenous leukemia only rarely responds whereas chronic lymphatic leukemia is benefited in approximately half the treated patients. Remissions are temporary. (See references previous paragraph.)

Hodgkin's disease has been treated in 36 cases and was clinically benefited for a short time in approximately half. (See previous references.) It is noted that Reed-Sternberg giant cells develop during therapy suggesting that the underlying disorder was unchanged.[137] The response in 13 cases of lymphosarcoma was more favorable—9 showing a temporary remission.[132, 38, 134]

Multiple myeloma has been treated in 25 patients.[138, 139, 140, 38, 134] However, even though Bence-Jones proteinuria ceases and the patient feels some better the course is usually unaltered. It must also be remembered that spontaneous remissions may occur in this disease.

Myasthenia gravis when combined with a thymoma is reported to improve as the thymoma is reduced in size by ACTH.[141] Other cases of myasthenia gravis usually become worse during therapy, but are claimed to be somewhat improved when therapy is stopped.[142] This lacks confirmation.[38, 143]

VI. METABOLIC DISORDERS

Idiopathic hypoglycemia has been treated in 5 patients with good effect.[144] In one patient ACTH was given for a year and then withdrawn without relapse. The excellent results in these patients are due to the diabetogenic effects of cortisone.

Nephrosis has been treated in 106 patients.[145, 146, 38, 147, 148, 149, 150] Loss of edema and reduction in serum cholesterol is common, but increase in blood proteins and abolition of albuminuria is rare. The diuresis usually begins 24 hours after stopping ACTH and reaches its maximum in 6-9 days.

VII. MISCELLANEOUS DISORDERS

Non-tropical sprue (idiopathic steatorrhea) has been strikingly benefited by cortisone.[151, 152] Arteriosclerotic obliterans has been moderately improved[38] due to the ability of cortisone to increase peripheral circulation. Similarly, Raynaud's disease may be ameliorated.[38]

SUMMARY OF PART I

The initial pessimism regarding the clinical usefulness of ACTH and cortisone has been replaced with enthusiasm as one disorder after another has been reported to be benefited. It is difficult to see what these disorders have in common that could explain their improvement with treatment. Certainly they are not examples of cortisone deficiency states. The classification presented here is obviously superficial. When more is known about intracellular metabolism it may be found that cortisone affects all these processes at specific vital points. Then a more logical classification will be possible.

In summary, principal indications for treatment with ACTH or cortisone are the true glucocorticoid deficiencies, acute collagen diseases, hypersensitivity states, inflammatory diseases of the eyes, joints, skin, intestine, severe toxic states, acute pulmonary fibrosis, acute leukemia or lymphoma and the special metabolic disorders—idiopathic hypoglycemia and nephrosis.

PART II

The Limitations of Adreno-Cortical Hormone Therapy

INTRODUCTION

Part I has summarized the uses of ACTH and cortisone. Statements which prompt caution have been common throughout these reports of dramatic improvement. The promptness and severity of return of the disease process upon stopping therapy has been discouraging in all but those diseases which are self-limited. Even in these there is doubt that the natural duration is materially shortened by treatment. The economic burdens of endless ther-

apy are often prohibitive. It appears that no disease is actually cured by ACTH or cortisone.

Since many of the diseases are otherwise fatal, undesirable complications of therapy may be of limited concern. However, with less serious disorders complications may constitute a greater threat than the original illness.

Therapeutically one seeks to give enough hormone to accomplish the desired clinical result without producing any undesirable effects. Unfortunately, both the desired and undesired actions are often "two sides of the same coin"—both being normal physiologic actions of the hormones. Thus, in contrast to other drugs, the undesired actions of ACTH and cortisone are not "side effects." There is no hope of avoiding them by obtaining a purer preparation.

Although undesirable effects are dependent upon dose and duration of treatment, the reported series agree that about half of all patients on full doses for more than two weeks develop complications. Hench noted undesired effects in 61%,[25], Margolis in 50%,[153] Kuzell in 65%,[154] Boland in 40%,[155] Thayer in 65%,[156] and Ward in 54%.[8] This incidence may be reduced by a reduction in dosage or duration of treatment.[157, 158, 159, 7] However, this frequently defeats the aims of therapy.

Table III outlines the reported undesirable effects of adreno-cortical hormone therapy. Each month additions are made to this list.

TABLE III

Undesirable Effects of Adreno-Cortical Hormone Therapy

I. Undesirable Nervous and Psychic Effects
1. Insomnia
2. Depression
3. Suicide
4. Euphoria
5. Tremor
6. Psychosis
7. Drowsiness
8. Convulsions
9. Delirium tremens
10. Neuritis
11. Anosmia
12. Olfactory hallucinations
13. Headache
14. Polyphagia
15. Coma
16. Tinnitus
17. Transitory deafness
18. Gustatory aberrations
19. Brain damage

II. Undesirable Endocrine Effects
1. Pituitary
   a. Basophile hyalinization
   b. Basophilic adenomata
   c. Inhibition of growth hormone, thyrotropin, gonadotropins
2. Adrenal
   a. ACTH overstimulation
   b. Cortisone atrophy
   c. Withdrawal adrenal insufficiency
3. Thyroid
   a. Corticogenic hypothyroidism
   b. Withdrawal hyperthyroidism
4. Gonad
   a. Loss of libido
   b. Amenorrhea
5. Pancreas
   a. Steroid diabetes
   b. Permanent diabetes

III. Undesirable Skin Effects
1. Acne
2. Hirsutism
3. Baldness
4. Furunculosis
5. Abscess formation
6. Sweating
7. Easy bruising
8. Purpura
9. Keratosis pilaris
10. Striae
11. Impaired wound healing
12. Pigmentation, generalized and focal

IV. Undesirable Body Fat Changes
1. Moon face
2. Buffalo hump
3. Protuberant abdomen

V. Allergy to ACTH and Cortisone
1. Local pain
2. Urticaria
3. Purpura
4. Rash
5. Fever
6. Erythema multiforme
7. Anaphylactic shock
8. Refractory state

VI. Undesirable Effects on the Eyes
1. Blurred vision
2. Glaucoma
3. Lacrimation

VII. Undesirable Effects on the Breasts
1. Gynecomastia (male)
2. Breast atrophy (female)
3. Accelerated breast carcinoma

VIII. Undesirable Effects on the Respiratory System
1. Deepened voice (female)
2. Pneumonia and tuberculosis
3. Sudden respiratory distress

continued on next page

IX. Undesirable Circulatory Effects
1. Hypokalemic cardiac effects
2. Hypertension
3. Increased peripheral resistance
4. TEAC floor increased
5. Hypertensive encephalopathy
6. Congestive failure
7. Edema
8. Thrombophlebitis
9. Mesenteric thrombosis
10. Portal thrombosis
11. Bleeding tendency

X. Undesirable Serological Effects
1. Intercurrent infection
2. Reactivate latent infection
3. Exacerbate existing infection

XI. Undesirable Hemocytological Effects
1. Leukocytosis
2. Marrow depression
3. Precipitate sickle cell anemia crisis
4. Accelerate certain acute leukemias and lymphomas

XII. Undesirable Gastrointestinal Effects
1. Unsuspected peptic ulcer
2. Unsuspected perforation
3. Unsuspected hemorrhage
4. Hypokalemic ileus

XIII. Undesirable Hepatic Effects (in cirrhosis)
1. Ascites
2. Intraabdominal hemorrhage
3. Portal vein thrombosis
4. Esophageal hemorrhage

XIV. Undesirable Renal Effects (in nephritis)
1. Increased renal work
2. Azotemia
3. Hyperkalemia

XV. Undesirable Muscular Effects
1. Weakness
2. Wasting

XVI. Undesirable Osseous Effects
1. Osteoporosis
2. Pathologic fracture
3. Withdrawal arthritis

I. UNDESIRABLE NERVOUS AND PSYCHIC EFFECTS

The undesirable nervous and psychic effects include at least three major complications—psychosis, suicide, and convulsions. Suicide has been reported several times,[160, 161, 50] in association with depressed states which may occur in as many as 35% of treated patients.[68] Psychosis, occasionally irreversible, usually schizophrenia, is a tragic complication which cannot be avoided since only one-third manifest pretreatment personality abnormalities.[162, 28, 163, 164, 165, 166, 103, 29, 167, 134, 136] Psychosis may appear after as little as a total of 200 mg. of cortisone.[167] Seizures occur in about 2%[162, 38, 168, 76, 69] and may be fatal.[149] They are usually preceded by a marked weight gain suggesting that water retention may play a role. Insomnia is reported in 30%.[38] Euphoria including impaired judgment, increased psychomotor activity and hypomania is seen in 9-39%.[38, 166, 156, 163, 8] Tremors,[168] drowsiness,[169] delirium tremens,[170] anosmia,[166] olfactory hallucinations,[156] gustatory aberrations,[156] tinnitus,[25] transitory hearing loss,[154] troublesome polyphagia,[38, 8] troublesome excessive libido, and headaches[38] are reported. Neuritis, manifested by paresthesias and paralysis, occurs.[38, 25, 166, 8] Brain damage has been reported clinically[76] and at autopsy.[171] Animal experiments verify hypothalamic and thalamic injury by ACTH and cortisone.[172] An abnormal electroencephalogram is produced or intensified in 85%.[173] In some instances this is due to hypokalemia.[174, 76]

II. UNDESIRABLE ENDOCRINE EFFECTS

Undesirable effects are reported on pituitary, adrenal, thyroid, gonadal and pancreatic function. Both ACTH and cortisone depress the endogenous release of ACTH from the pituitary causing hyalinization of pituitary basophiles (Crooke's cell changes) and formation of basophile adenomata as seen in Cushing's disease.[175, 176] Other pituitary hormones may be either suppressed or their effects neutralized. Growth hormone effects are inhibited by cortisone.[177, 178, 179] The thyrotropic and gonadotropic hormones may be depressed. (See below.)

Undesirable effects on the adrenal gland include the possibility of overstimulation by ACTH as mentioned in Part I. Contrariwise cortisone causes adrenal atrophy.[180] When either ACTH or cortisone are stopped symptoms of adrenal insufficiency ensue in some patients. Weakness, fatigue, hypotension, arthralgia, nausea and vomiting are reported in 9%.[156, 119] During this period of a few days to a few weeks the tests of adrenal function show insufficiency—17-ketosteroid excretion falls to low levels, the Thorn eosinopenia test is unresponsive, an excessive sodium and water diuresis may occur.[181, 182, 156] Sudden crises are reported.[183, 7] A severe relapse of the disease being treated may leave the patient more disabled than before treatment.[48, 184]

It is claimed that corticogenic hypothyroidism occurs in 80% of all treated patients as measured by protein bound iodine and I-131 uptake.[185, 186, 187, 188, 215] The addition of 30 mg. of thyroid per day may improve or restore the clinical response of the patient to ACTH or cortisone.[189, 190, 160] The BMR is of little value in diagnosing corticogenic

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The RHODE ISLAND MEDICAL JOURNAL

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RHODE ISLAND INFANT AND MATERNAL MORTALITY

ACCORDING TO preliminary figures released by the National Office of Vital Statistics of the Public Health Service, infant and maternal mortality rates continued to decline in 1951. Infant deaths last year fell to a new low of 28.8 per 1,000 live births and maternal deaths dropped to 7 per 10,000.

It is a source of satisfaction that the Rhode Island rates have followed this trend. For example: our maternal mortality in 1948 was 11.1 per 10,000 and 4.1 per 10,000 in 1951. Infant mortality has declined from 25.4 per 1,000 in 1948 to 23.9 per 1,000 in 1951.

Although these are accomplishments of which the medical profession can be proud, there are many ramifications in tabulating and reporting which need clarification, for example: the reporting of prematurity in Rhode Island has not always conformed to the criteria of the Department of Health. Infants weighing as little as two pounds eleven ounces have been reported as mature. If our figures on premature death rate and neonatal mortality are to mean anything, Rhode Island physicians and hospitals must adhere to the definition of prematurity as recommended by the American Academy of Pediatrics and accepted by the Rhode Island Department of Health for the purpose of reporting premature births. The arbitrary weight of 2500 gms. (5½ pounds) has been selected as the division between maturity and prematurity. In 1950 there were 586 infants weighing less than 5½ pounds, the birth reported as mature.

The greatest loss of life associated with birth is caused by prematurity. Improvement in the premature death rate has not kept pace with that of either maternal mortality or the overall infant mortality rate. Improvement in the premature death rate has come largely as a result of improved pediatric care. There has been little reduction in the incidence of prematurity. Our present medical knowledge, supported by such auxiliary services as education to encourage early prenatal care, dieticians, social service workers and public health nurses may offer a partial solution to this problem.

THANK YOU, MRS. CARMARK

For fifteen years Mrs. James C. Carmark has been the guiding light and leader of the Field Army of the State Cancer organization. Anyone who has been in touch with cancer education and cancer control in general in this State knows that she has been a prodigous worker, a remarkably well-informed person on all matters connected with the cancer work, and that she has been able to impart her enthusiasm to a great number of helpful women workers.

Starting in the late thirties, Mrs. Carmark practically single-handed developed the Women's Field Army which carried on an annual campaign for funds, and then devoted the remainder of the year to judicious use of those funds to carry the important information regarding cancer signs to the general public. The task was most difficult in the early days of her pioneering in cancer education, and it was only when the nation at large became aroused through national publicity that the cancer campaign funds reached a total that permitted the employment of staff personnel.

The present enlightened state of mind of the average citizen regarding cancer, and the fact that many persons living today owe their continued existence to the tireless and unending education campaign of the Field Army, are achievements that should make Mrs. Carmark look back with pride and joy on her accomplishments as she now retires from her role as Rhode Island's foremost volunteer health educator.

SAFETY ON JULY FOURTH

In 1941 the Providence Medical Association took active leadership in focusing attention on the mounting toll of injuries in this State due to injuries from fireworks and explosives on July 4. Out of that campaign came a strong demand for legislation to make for a safe and sane celebration of Independence Day by placing the use of fireworks under strict controls.

The effect of the law was immediate. In 1941 there were 141 injuries reported by the hospitals. In 1942 when the law was first in effect there were ONLY 4 MINOR INJURIES.

In the past few years, however, the problem has again arisen, due in no small measure to the transportation of fireworks by individuals into this State after making purchases in the neighboring areas of Connecticut, in particular.

A check of the hospitals of the State this past month on the reported accidents or injuries treated over the 4th shows 21 cases, of whom three were for eye injuries, and eighteen for burns or lacerations.

The enforcement of our statutes has been good, to our best knowledge. The problem appears to be the education of our good neighbors in the adjoining States to the dangers inherent in the general sale of fireworks. Here is an outstanding example of where an inter-state conference of community leaders could render a great service to everyone in accident prevention.

SILVER THREADS AMONG THE GOLD

Much has been written in the press about the British National Health Service, and in particular of the great cost of this service.

Unnoticed for the most part in this country has been the overall picture of the British National Insurance program. The debates in the House of Commons this Spring regarding social security questions are worthy of comment when one considers the extensive programs already under way in the United States, and the recent increase in social security benefits to the persons in the older age brackets.

In Britain the Government's proposals had two main aspects. First, it proposed raising payments under the national insurance system to meet the increased cost of living, paralleling the increases granted in national assistance rates. Secondly, it sought to restore uniformity among the great variety of payments that are made under the insurance system. Uniformity of benefit had always been an objective of the system, and had been affected mainly by changes in retirement pensions in 1951.

While the proposals met with general support from all sides of the House, the debates took up some of the deeper social security questions, in particular those certain to affect the program in future years. The most serious problem proved to be the staggering burden of retirement pensions on the social security finances.

Nearly 68% of the Fund now goes to the old age payments, and the burden is increasing annually because of higher rates of benefit and greater longevity. The British experts freely estimate that by the end of the next five years the insurance fund will show a deficit of one hundred million pounds, and this figure will rise to more than four hundred million by 1977, unless some action is taken prior to that time to correct the situation. It is apparent that the future will witness a change in the retirement age as a means of reducing the financial burden, and efforts will have to be directed to continued employment for the old aged people so that the younger age population will not be saddled with the mounting tax burden. The decisions will not be easy ones to make, particularly for the politicians with their rosy promises of a utopian existence for everyone through the medium of so-called social security benefits.

What about the United States and this problem?

As of June a year ago the Federal Security Agency reported about four million people to be receiving benefits under our old age and survivors insurance program. Two million of them were retired workers, and another million were the wives and dependent husbands of retired workers and widows, dependent widowers, and dependent parents of workers who had died. Of the remaining million, 200,000 were young widows and 800,000 were children.

This certainly does not represent a great financial burden today in view of the high employment and

continued on next page

high wages throughout the country. But in June, 1951, about 12.7 million people in the United States were 65 or over. About a third were working or were wives of men who were working. Of the remaining 8.8 million, about one-third were getting old age and survivors insurance benefits. While employment continues American people prefer to work rather than retire, and therefore the insurance fund is apparently ample.

But persons over 65 years are rapidly increasing in numbers, and in relation to the total population. It is now estimated that by 1975 we will have approximately 20 million persons aged over 65, a probable 10.8 per cent of our population.

With the present staggering tax burden in a time of high employment, and with the social security program continually expanding, and increasing benefits as was done by Congress in its recent session, we will do well to look far into the future.

The youth of this country is now saddled with a national debt that shows no sign of decreasing. The day may come when the present employed population will demand the benefits of old age retirement for which they are now being taxed, and the financial burden could be too great to be met. The result could be catastrophic for both the then employed public, as well as for the older aged group whose dream of financial security in their later years would be shattered by reduction of benefits and the altering of the retirement age.

HEALTH INSURANCE

At the fifth international education conference of the United Automobile Workers-CIO, held in Cleveland last April, three United States Senators discussed the morality of Congress and answered questions from the floor propounded by workers. Only one question was asked about national health insurance, and U. S. Senator Hubert Humphrey of Minnesota answered it as follows:

I have always favored the health insurance principle, and I will continue to do so. I have believed that the first job that we have is the tooling up of our medical facilities, the expansion of our hospital plant, our out-patient clinics. Particularly is this true in the rural areas of the United States.

I also believe we have got to keep in mind the administrative difficulties that confront us, and therefore it appears to me that the programs which we have launched upon such as group health and many of the employer-union contracts are a good beginning and a good laboratory for the experimentation that we need.

There is no use of talking about incorporating everybody into a massive nationwide health insurance program until you have the facilities, the tools, the techniques, the technicians, the doctors and the whole program of medical science that is so vital to proper medical care.

There is one big word missing from Senator Humphrey's answer. That word is VOLUNTARY. Everyone favors the insurance principle, but which type — compulsory or voluntary? Everyone with any experience in insurance recognizes the administrative difficulties facing the country in developing nationwide programs. Senator Humphrey speaks of the uselessness of trying to incorporate everyone into a massive nationwide health insurance program until there are enough hospitals, doctors, and technicians. There is clear inference in this remark that the Senator considers a compulsory national health system favorably, and that he feels it cannot be initiated until there are sufficient facilities and personnel to administer it.

But what of the voluntary system of health insurance that has developed with such amazing success in the past decade? The principle of voluntary insurance has won the support of the vast majority of the people of this country, but to hear such spokesmen as Senator Humphrey one would get a far different view.

The annual survey of accident and health coverage in the United States, released in June by the Health Insurance Council which consists of nine associations in the insurance business, which in turn are made up of companies writing health coverages, is most revealing.

In 1941 approximately 15 million people had hospitalization expense protection. At the end of 1951 the total was more than 85 million.

In 1941 there were less than 8 million people protected against the cost of surgical care. By the end of 1951 the number of persons protected was 65½ million.

An estimated 3 million had some medical expense coverage ten years ago. By the end of 1951 the number was close to 28 million.

This dramatic development in health coverage on a voluntary basis during the past ten years is clear indication of the desire of the people of this country to help themselves as far as possible to meet the costs of sickness. Senator Humphrey might well have ended his remarks above with the statement "There is no use of talking about incorporating everybody into a massive nationwide health insurance program."

The development of our own Physicians Service, and of the Rhode Island Plan sponsored by the Society, directs our personal attention to the health insurance coverage in Rhode Island. According to the survey of the Health Insurance Council the

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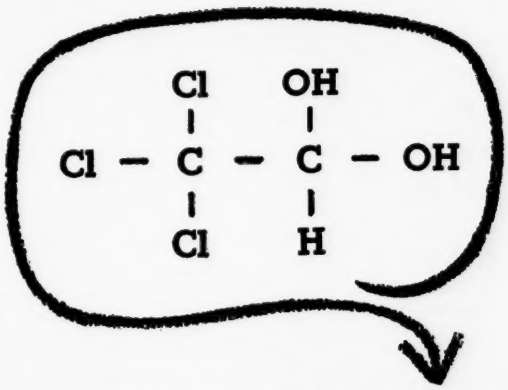

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1. Hyman, H. T.: An Integrated Practice of Medicine (1950)
2. Rehfuss, M. R. et al: A Course in Practical Therapeutics (1948)
3. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics (1941), 22nd printing, 1951.
4. Sollman, T.: A Manual of Pharmacology, 7th ed. (1948), and Useful Drugs, 14th ed. (1947)

HEALTH INSURANCE

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following figures, for the end of 1951, are given for this State:

Number of People Protected as of December 31, 1951

Hospital	*Surgical*	*Medical*
654,000	381,000	307,000

In the first six months of the current year Physicians Service has enrolled an additional 43,000 for both surgical and medical protection. No figures are available at this writing on 1952 sales by insurance companies, although we know some business has been written.

These figures exclude those protected by workmen's compensation insurance, persons in the armed forces, those receiving medical care and disability pensions under certain conditions to war veterans, and those persons in public institutions.

It is readily apparent that an overwhelming majority of Rhode Island's 791,896 citizens prefer to provide their own sickness and accident protection on a voluntary basis, and in that expression of freedom they are strongly supported by millions of citizens of the other States as evidenced by the Health Insurance Council's survey.

CIVILIAN MEDICAL CARE OF ARMY PERSONNEL

It has come to the attention of this headquarters that in several instances bills for civilian medical care of Army personnel have been addressed to the Commanding General, First Army.

In order for bills of this nature to receive immediate attention, it is requested that doctors or hospitals submitting bills for treatment of Army personnel submit the bills to:

The Surgeon
First Army
Governors Island
New York 4, N. Y.

As a means of advising members of the State Medical Society regarding submission of bills incurred by Army personnel, publication of the following notice in the official publication of your organization would be very much appreciated.

"Bills for authorized medical care and treatment of Army personnel should be submitted to the commanding officer of the organization to which the patient belongs, or to the military authority who provided the authorization for the medical service. If the location of these individuals is not readily known, the bill should be sent to the military authority listed below."

For services rendered in the following States:

FIRST ARMY AREA		Submit bills to:
Connecticut	New Jersey	The Surgeon
Maine	New York	First Army
Massachusetts	Rhode Island	Governors Isl'nd
New Hampshire	Vermont	N. Y. 4, N. Y.

Yours truly,

PAUL A. KEENEY, Colonel, MC
Deputy Surgeon, Headquarters First Army
Governors Island, New York.

17 June 1952

DERMATOLOGISTS ELECT

At the annual meeting of the Rhode Island Dermatological Society held recently Dr. Carl D. Sawyer was elected President and Dr. Malcolm Winkler, Secretary.

GAMMA GLOBULIN IN PREVENTION OF PARALYTIC POLIOMYELITIS

(The following statement submitted by the Chairman of the Sub-Committee on Blood of the Health Resources Advisory Committee has the approval of the Committee on Blood Banks of the American Medical Association)

Whether gamma globulin will be effective in the prevention of paralytic poliomyelitis is not now known. On the basis of animal experiments and preliminary study on humans, it is possible that globulin will have value in human poliomyelitis, but serious questions remain to be answered before such a hope can be substantiated. Nevertheless, public dissemination of information on the status and objectives of current studies, incompletely presented or misunderstood has created a serious demand for gamma globulin which cannot be met.

Virtually the entire output at current production rates is required to meet the demand for prevention or modification of the course of measles and infectious hepatitis.

Under the circumstances, it is obvious that the existing limited supply and current production of gamma globulin should be reserved for use in these diseases in which its efficacy has been established.

CARDIAC SURGERY*

HARRIS B. SHUMACKER, JR., M.D. *of Indianapolis, Indiana.*

The Author. *Harris B. Shumacker, Jr., M.D., of Indianapolis, Indiana. Chairman, Department of Surgery, Indiana University Medical School.*

THE PAST quarter of a century, and particularly the latter half of this period, has witnessed considerable progress in the surgical treatment of disorders of the heart. In a brief review it is impossible to give credit to all who have participated in this advance but certainly it has in large measure resulted from the contributions of Beck, Gross, Blalock, Crafoord, Brock, Harken and Bailey.

Prior to the first successful ligation of a patent ductus arteriosus by Gross in 1948, patients with congenital anomalies of the heart and great vessels were of necessity managed only by watchful waiting. Now at least a number of these malformations can be treated with great satisfaction by surgical measures.

Through children with patent ductus arteriosus generally appear to be relatively normal and rarely get into real difficulty early in life, they have a poor ultimate prognosis. Without treatment their life span is shortened appreciably and they are always threatened with cardiac failure or subacute bacterial endarteritis. Most of my patients have fortunately been operated upon before frank failure developed. In general, the older group manifested more symptoms of poor cardiac reserve than the younger patients. That cardiac failure is not, however, necessarily a late development is evident. I have treated one little boy of 5 who had been in chronic failure and on digitalis therapy for over a year. Digitalis was stopped 5 days after operation and he was restored to excellent health. Only about one in 25 of our patients had had endarteritis before surgery. A number, for some peculiar and poorly understood reason, have a real stunting of growth. This effect is well illustrated by one of my patients who was admitted to the hospital at the age of 10 months as a nutritional problem. She weighed only 9.5 pounds, little more than her birth weight. The only positive physical and laboratory findings were those of patent ductus arteriosus. She gained 2.5 pounds, an increase in weight of over 25 per cent, during the first three and a half months after operation.

Almost three-quarters of my patients have been females. At the time of operation they have ranged in age from 10 months to 36 years. About one-fourth have been 3 or younger, about 70 per cent 10 or younger and 12.5 per cent 20 or older. The physical signs have been typical in most of them. In one out of 8, however, the diagnostic problem has been somewhat more difficult. In some of these exceptional cases the murmur was not continuous but instead there was a long systolic murmur followed by a pause and then by a diastolic murmur. In some only a systolic murmur was audible. If the diagnosis seemed questionable, cardiac catheterization was generally carried out. The electrocardiogram was essentially normal in about three-fourths. In 18 per cent there was definite or suggestive evidence of right ventricular hypertrophy and in only 7 per cent was there evidence of left ventricular hypertrophy.

The operative mortality in patent ductus arteriosus not associated with a more severe anomaly such as coarctation of the aorta or transposition of the great vessels was a little less than 2 per cent. At first the patients were treated by the multiple ligation-transfixion technique of Blalock. Two experiences, however, prompted me to abandon this policy in favor of division and suture. One was a 16-year-old girl who, some months after uneventful surgery, developed left recurrent laryngeal paralysis and hemoptysis as the result of a small aneurysm which appeared at the aortic end of the ligated ductus. Fortunately it was possible in this case to excise the aneurysm and close the opening in the aorta.* The second patient did not fare so well. She was a 20-year-old woman who, one month after operation, developed evidence of recanulization with formation of an aneurysm in the region of the ductus associated with a staphylococcus aureus bac-

* From the Department of Surgery, the Indiana University Medical Center, Indianapolis, Indiana. Aided in part by a grant from the James Whitcomb Riley Memorial Association.

Presented at the 141st Annual Meeting of the Rhode Island Medical Society, at Providence, R. I., May 7, 1952.

*This procedure was performed by G. E. Lindskog of New Haven.

continued on next page

teriemia. The organism was resistant to all drugs. Unfortunately she died of ventricular fibrillation just as the thorax was entered in the hope that surgical extirpation of the aneurysm might be possible. It is my feeling that the practice of division and suture gives the patient assurance of a permanent cure and does not add to the risk of operation. Except for the exceptional cases mentioned, all, whether treated by ligation or by division, have had an excellent result.

Coarctation of the aorta, like patent ductus arteriosus, is generally not associated with distressing symptomatology early in life but carries a poor prognosis as far as longevity is concerned. My experience is based upon 25 cases. Two had had subacute bacterial endarteritis and one of them also had an aneurysm of the distal aorta. In this case the blood stream could be sterilized with penicillin beforehand and it was possible to excise the area of coarctation together with the aneurysm and restore continuity by end-to-end aortic suture. Most of those treated in adult life had symptoms referable to hypertension. One case deserves brief mention, a 28-year-old woman who had been practically bedridden for one year because of dizziness and headache. She had palpitations, tachycardia and dyspnea on exertion, was easily fatigued, and noted difficulty with her vision. She had papilloedema, poor renal function, reduced renal blood flood and some elevation of non-protein nitrogen. After excision of the coarctation, which was a complete diaphragm without lumen, her symptoms disappeared promptly, blood pressure returned to normal, the papilloedema subsided, and renal function became normal.

Four of our patients were 6 or younger, six were between 8.5 and 11.5, one was 16, five were 17 or 18, seven were in their twenties and two in their thirties. The area of coarctation was excised and a repair carried out in all except one fatal case. The subclavian was anastomosed to the distal aorta in 4 cases and an aortic reconstruction was performed in 20. There were 3 deaths, all due to technical difficulties or a complication of anesthesia. One cannot help feeling that they were preventable. One patient whose proximal aortic segment was long and hypoplastic had a poor result as far as restitution of normal blood pressure and circulation to the lower extremities was concerned and one of those in whom a subclavian-aortic anastomosis was made was only moderately benefited. Good results were obtained in the remainder. It is apparent from my experience, as it is from those experiences reported by others, that it is important that the diagnosis be made early in life and operation carried out in childhood.

Tetralogy of Fallot differs from coarctation of the aorta and patent ductus arteriosus in that symptoms are marked and usually incapacitating from infancy. I have recently reviewed 74 operative procedures performed upon 68 patients. This series does not include earlier cases performed at the Johns Hopkins Hospital and included in reports from that institution, nor exploratory operations in which the patient was found to have some other condition such as truncus arteriosus or transposition of the great vessels. It is clear that the operative mortality could be kept at a minimum and the percentage surviving with marked benefit increased if cases were carefully selected and infants in dire distress and those with such complications as brain abscess and hemiplegia were excluded. It is my feeling, however, that operation should not be denied any of these pitifully handicapped children and no patients have been rejected though infants under one and a half have not been treated unless symptoms were so severe as to make delay of surgery unwise.

Nine postoperative deaths occurred, an operative mortality of 12.2 per cent and a case mortality of 13.2 per cent. Four patients are known to have died subsequently, 2 from causes related to, and 2 from causes unrelated to, the anomaly and its surgical correction. Thus, 81 per cent are alive and most of them are in excellent health. Thirteen patients were under one and a half years in age. Three died, a mortality of 23 per cent. One with an excellent result from a Potts' aortic-pulmonary anastomosis subsequently developed heart failure some months afterwards and succumbed within a few days. Another with excellent improvement following surgery subsequently died of a subdural hematoma. The operative procedure brought about a good result in all the survivors save one. In this patient a second operation was performed a year later and a fairly good result was obtained. Sixty-one operations were performed upon 55 patients more than a year and a half in age. The subclavian-pulmonary artery anastomosis of Blalock was carried out in most of the patients. The Potts' procedure was performed in 13. Three were treated by pulmonary vavulotomy or dilatation of a stenotic pulmonary artery. There were 6 deaths, an operative mortality of 9.8 per cent and a case mortality of 10.9 per cent. It is of interest that two of the 6 deaths were in patients who had no pulmonary artery on the side upon which the thoracotomy was performed and that in a third whose pulmonary artery tore irreparably after completion of a pulmonary-aortic anastomosis the pulmonary artery was grossly paper thin and histologically showed marked hypoplasia of elastic tissue and muscular components. Two patients have died subsequently, one of aspiration atelectasis during an upper respiratory infection, and one of a brain abscess which was probably present before operation when the neurological symptoms present were thought due to cerebral

thrombosis. Over 85 per cent are living and most of them are remarkably improved.

The benefit from operative treatment is so striking it can hardly be appreciated by those who have not seen such patients beforehand and afterwards. The cyanosis disappears or becomes very faint and instead of having marked limitation of physical activity the patient can lead a life which is normal for all practical purposes. Many of the children can engage in such strenuous sports as basketball, hockey and skiing.

Reported experiences with Brock's ingenious valvulotomy procedure for pulmonic stenosis not associated with ventricular septal defect are not numerous. The functional results have been good but the operative mortality significant, 8 of the 47 cases recorded in the literature having died. My experience has been limited to 8 cases. No deaths occurred and all had a most gratifying result. Experience in our clinic indicates that great benefit is derived not only in the severe cases but in the milder cases as well. The milder cases present a more difficult diagnostic problem. They do not have the marked right ventricular enlargement, the hugh non-pulsatile pulmonary trunk segment, the pulsating liver and the high electrocardiographic P waves commonly present in severe cases. Cyanosis is apt to be mild, clubbing mild or absent, and hemoconcentration is uncommon. In such cases it is almost mandatory that cardiac catheterization be performed and this procedure yields data of diagnostic significance. Since, particularly in cases without marked right ventricular hypertrophy, it is not infrequently difficult to dislocate the heart into the left thorax so that the traction sutures can be placed accurately in the right ventricular wall preliminary to cardiotomy and valvulotomy, I prefer a mid-line sternal-splitting approach to the anterior thoracotomy which has been used by others. This approach gives excellent exposure of the anterior surface of the right ventricle and of the pulmonary trunk. All of the patients have been remarkably improved following operation.

Anomalies of the great vessels resulting in vascular rings which cause tracheal obstruction or dysphagia can be treated with success by operative severance of the ring as was first demonstrated by Gross. The commonest malformations producing such vascular rings are the double aortic arch and the anomalous right subclavian artery arising from the descending aorta on the left and passing to the right behind the esophagus. These are conditions which should be kept in mind whenever one is confronted with an infant who has respiratory difficulty or dysphagia.

Among the congenital cardiac difficulties for which no really satisfactory operative treatment is available are the atrial and ventricular septal defects and transposition of the great vessels. The placement of fascial sutures through the septum as suggested by Murray does not bring about complete closure of septal defects but is said to result in some benefit. The production of surgical defects of the atrial septum and end-to-end subclavian-pulmonary anastomosis proposed by Blalock and Hanlon for cases of transposition has brought about modest improvement in some cases. I have had no experience with the clinical application of these measures.

One of the great advances of recent years is the procedure of commissurotomy for mitral stenosis for which Bailey and Harken deserve great credit. My experience has been limited but has conformed to that of others. The chief contraindications appear to be active rheumatic fever, marked mitral insufficiency, and associated aortic valvular disease. The ideal case is the relatively young person without notable over-all cardiac enlargement and with evidence of a purely stenotic lesion or one associated with only mild insufficiency. In the more favorable cases the results are spectacular. I have had a few patients with an apparent pure stenosis in whom after finger-fracture of the fused commissures there is no residual cardiac murmur and the patient is seemingly entirely well. In spite of the good results which may be obtained, it must be kept in mind that one will meet with disappointment on occasions at the time of operation. If there is an extensive mural thrombus adherent to the atrial wall and the appendage, one may have no safe portal of entry into the atrium. From time to time one will find the valve to be a generally contracted conical valve instead of the usual one with fusion at the commissures and little or nothing can be accomplished. Furthermore, unless one limits his cases to the most favorable ones he will sometimes find he has explored a patient in whom the problem is principally one of insufficiency rather than stenosis. In spite of these disappointments, the results in general are most gratifying.

As experience has increased with the operative treatment of hypertensive disease by surgical measures it has become more and more apparent that after surgery patients have an augmented chance of survival and a decreased tendency for the development of cardiovascular complications. Those in whom there is hypertensive heart disease tend to undergo some decrease in heart size and improvement in cardiac function. If angina is present and the sympathetic denervation is extended upward to include the upper dorsal ganglia and the stellate ganglion, as is my policy, the patient is relieved of his pain.

Angina not associated with hypertension similarly responds well to sympathetic denervation, as was pointed out some years ago by White. In such

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cases it is my preference to destroy the sympathetics by alcoholic infiltration rather than by surgical extirpation. I am convinced that the relief of pain in cases of severe angina is most worthwhile. A number of procedures have been proposed in an effort to revascularize the ischemic myocardium in instances of coronary infarction. I have had no experience with them.

Considerable advances have been made in the operative management of chronic constrictive pericarditis. In the first place, it has become increasingly apparent that the pericardial resection should be very extensive. There is still some disagreement as to precisely what segments of the pericardium must be removed in order to relieve the cardiac disfunction. The experimental production of localized pericardial constriction and the evaluation of cases before and after operation by cardiac catheterization are doing much to clarify this problem. In the second place, Holman and Willett have demonstrated that pericardiectomy can apparently be performed in the presence of active tuberculous infection at a time when the operative procedure is safer, easier and more effective.

Recent experiences have demonstrated that foreign bodies may be removed from the heart with remarkable safety. The problem of acute cardiac tamponade resulting from wounds of the heart has been furthered by the experiences of Blalock and Ravitch. They have demonstrated that many of those who survive to reach a surgeon have wounds sufficiently small that they cease to bleed without cardiac exploration and suture. Often in such cases pericardial aspiration is all that is required.

Finally a word should be said about the cardiac dysfunction associated with large arteriovenous fistulas. In the presence of such a lesion the heart is subjected to considerable strain. The cardiac output is increased, the total blood volume increases and the heart becomes dilated. If treatment is not carried out frank failure may develop. In reviewing a large series of cases of arteriovenous fistulas Stahl and I found that definite cardiac enlargement developed early in about half of them and a comparable number underwent decrease in cardiac frontal area after resection of the fistula. The larger the fistula and the parent artery the greater is the likelihood of cardiac enlargement. Fistulas involving the femoral vessels, for example, are early associated with demonstrable increase in the cardiac frontal area in nearly 80 per cent of cases. No cardiac condition is subject to more satisfactory treatment than that secondary to a peripheral arteriovenous fistula, for cure of the fistula brings about dramatic improvement in cardiac dynamics. It is a procedure comparable to the relief of thyrotoxic heart disease by proper medicinal or surgical management of the thyrotoxicosis.

I have reviewed some of the recent developments in the field of surgery of the heart and great vessels. It is apparent that great strides have been made. There is every reason to believe that progress will continue.

Next meeting of the

PROVIDENCE MEDICAL ASSOCIATION

MONDAY, OCTOBER 6

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PROLUTON PRANONE

5th ANNUAL CANCER CONFERENCE FOR PHYSICIANS

Under the Auspices of the

RHODE ISLAND MEDICAL SOCIETY

WEDNESDAY, OCTOBER 15, 1952

At the Memorial Hospital Pawtucket, Rhode Island

11:00 a.m. EARLY DIAGNOSIS OF CANCER OF THE LUNG

Richard H. Overholt, M.D., *of Boston, Mass. Clinical Professor of Surgery, Tufts College Medical School.*

11:30 a.m. AIR POLLUTION AS A CANCERIGENIC FACTOR

W. C. Hueper, M.D., *Chief, Cancerigenic Research Studies Section, Cancer Control Branch, National Institute of Health, Bethesda, Maryland.*

12:00 noon UTERINE CANCER — THE PROBLEM OF EARLY DIAGNOSIS (A Motion Picture)

1:00 p.m. Luncheon at the Hospital

2:00 p.m. WHY DETECTION CLINICS?

Elmer Friedland, M.D., *of Buffalo, N. Y., Medical Director, Cancer Detection Center, Edward J. Meyer Memorial Hospital, Buffalo.*

2:30 p.m. RELATION OF BENIGN LESIONS OF THE BREAST TO THE DEVELOPMENT OF CARCINOMA

A. Purdy Stout, M.D., *of New York, Professor of Pathology, Columbia University College of Physicians and Surgeons.*

3:00 p.m. THE PROBLEM OF PIGMENTED MOLES AND MALIGNANT MELANOMA

George T. Pack, M.D., *of New York City, Clinical Professor of Surgery, New York Medical College.*

3:30 p.m. THERAPY OF MALIGNANCY IN CHILDHOOD

Sidney Farber, M.D., *of Boston Mass. Pathologist-in-Chief, Children's Hospital; Professor of Pathology, Harvard University.*

4:00 p.m. GENERAL DISCUSSION

THE PRESENT STATUS OF ADRENOCORTICAL HORMONE THERAPY

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hypothyroidism because cortisone causes a nonspecific increase in metabolic rate. After treatment is stopped two observers report the appearance of thyrotoxicosis which may have been related to therapy.[191, 192]

Gonadal effects as manifested by a loss of libido in the male and amenorrhea in the female are reported in 2-7%.[162, 38, 193, 166, 8, 153] Testicular atrophy may be expected from animal experiments,[177, 194] but has not been reported clinically. Virilism in female children[38] and deepening of the voice in the female[193] are reported.

Undesirable effects on the pancreas may be mediated by the high blood sugar and induced insulin resistance which are thought to result from impaired glucose oxidation and resulting increased gluconeogenesis as described in Part I. Corticogenic diabetes occurs in 10-20% depending upon dosage.[282, 38, 153, 166] Renal glycosuria also may occur.[281] Pre-existing diabetes is uniformly made more difficult to control although ketoacidosis is uncommon.[280] Urinary glycosuria may exceed the total daily carbohydrate intake.[195] Insulin resistance may be severe. The carbohydrate metabolism may remain abnormal for a month after treatment is stopped[196] but permanent diabetes as seen in the "Young dog" has not been encountered by Thorn,[61] Sprague,[162] or Engle.[197] However, having seen two such patients, one of which died of uncontrolled diabetes two months after stopping ACTH,[198] the vigorous use of insulin to protect the pancreas is recommended. Others also report persistent diabetes.[166] Rat experiments confirm the possibility of permanent corticogenic diabetes.[199, 200]

III. UNDESIRABLE SKIN EFFECTS

Undesirable effects on the skin occur in about 16%.[166, 201] Acne, which may be cystic and leave permanent scarring, occurs in 12-17%.[38, 103, 156, 153] Loss of head hair, another adrenal androgenic effect, is reported.[28, 153, 156, 202] Cortisone ointment applied locally impairs hair follicle activity experimentally[203] but did not impair regrowth of shaved forearm hair.[198]

Furunculosis is noted in 11%;[168] sweating in 5-11%;[38, 155, 8] purpura in 5%.[155] The occurrence of keratosis pilaris[193] may be due to Vitamin A deficiency since ACTH causes a diuresis of vitamin A.[204]

Hyperpigmentation occurs in 2-32%.[38, 55, 153, 205] There may be a generalized darkening of the skin,[156, 205] new junctional nevi,[205] spots on dorsum of hands,[206] pigment bands on nails,[177] pigmentation of scars, nipples and axillae. If this be due to melanophore hormone contamination of ACTH as has been suggested by Sprague[193] it fails to explain why cortisone will also cause pigmentation. Why such pigmentation does not occur in natural Cushing's syndrome but does during therapy is also unknown.

Striae which may be irreversible and unsightly, occur in 3%[8] and are probably due to protein catabolism weakening the subcuticular fibrous tissue.

A similar explanation is offered for the impairment in wound healing[207, 208, 209] which is noted in 20% of biopsy wounds made before or during therapy.[38, 156] Decubitus ulcers may appear in young patients.[210] An induced vitamin C deficiency may precipitate scurvy with hemorrhages and poor healing.[211, 212]

Abscess formation and impetigo may follow injection of either ACTH or cortisone.[156]

IV. UNDESIRABLE BODY FAT CHANGES

Moon face is reported in 7-65%.[38, 213, 166, 103, 156, 8, 214] The cervicodorsal "buffalo" hump and protuberant abdomen may also occur after prolonged therapy.

V. ALLERGY TO ACTH AND CORTISONE

ACTH is antigenic[216] and may cause reactions in about 3%[38, 217, 165, 218, 219, 220] manifested by local pain, urticaria, purpura, rash, fever, and erythema multiforme. Exfoliative dermatitis may result and will respond to cortisone.[221] Acute anaphylactic shock is reported in 3 of 10,000 injections.[222] Some patients are not only sensitive to hog ACTH, but also to sheep and bovine ACTH. One case is reported who was also sensitive to the protein-free polypeptide ACTH prepared by Li.[223] Such an occurrence may explain the refractory state seen in some patients who no longer respond to treatment.[224]

Contrariwise cortisone has not been reported to be antigenic and it will control reactions caused by ACTH. Rare reactions following cortisone injection are probably due to the vehicle.

VI. UNDESIRABLE EFFECTS ON THE EYES

The undesirable effects of therapy on the eyes

include blurred vision in 2-12%.[38, 25, 155] This is presumably due to an acute myopia due to swelling of the lens with cortisone induced water retention. It is possible that this same retention and swelling may precipitate an attack of glaucoma in a predisposed individual.[23] Lacrimation is increased.[156]

VII. UNDESIRABLE EFFECTS ON THE BREASTS

Gynecomastia may occur in the male[169, 59, 225] and contrariwise atrophy of the breasts in the female is reported.[156] Breast carcinoma growth appears to have been accelerated in one case.[226]

VIII. UNDESIRABLE EFFECTS ON THE RESPIRATORY SYSTEM

The papillae on the posterior third of the tongue may show striking hypertrophy.[156] Respiratory infections, especially pneumonia and tuberculosis are prone to develop (see below). Dramatic respiratory distress may occur upon stopping therapy.[183]

IX. UNDESIRABLE CIRCULATORY EFFECTS

Hypokalemia, with EKG changes,[227] occurs in over half of treated patients who do not receive proper potassium supplements.[38] Cortisone-induced rheumatic-like heart lesions seen in animals[199, 200] can be prevented with potassium chloride ingestion.[228]

Hypertension occurs in 5-31%,[38, 166, 156, 103, 153] and is especially frequent in patients with renal damage—60%:[229, 156, 45] It may cause fatal encephalopathy.[213, 230, 120] Hypertension probably results from an increase in peripheral resistance,[231, 232] An increased stroke volume[171] plays only a minor role and an alleged increase in blood volume[233] may not occur. The TEAC floor rises.[231] Cortisone is less prone to cause hypertension than ACTH and does so only if renal damage is present.[229]

Edema formation is common—18-57%.[38, 213, 68, 153]

Congestive failure may occur if there is heart disease. It may be very resistant to digitalis[29] but diuresis with mercurial diuretics is ordinarily effective.

Elevated cholesterol and lipids in 20-60% may theoretically hasten atherosclerosis.[234, 235, 236, 7]

Opinion is divided concerning the effects on the clotting mechanism. On the one hand it is claimed that thrombophlebitis is noted with increased frequency during and after therapy—1-6%,[78, 237, 166, 156, 8] including fatal pulmonary emboli.[238] Of 700 treated patients, 28 developed 40 thromboembolic episodes; 45% during therapy and 55% during withdrawal of therapy.[239] Anticoagulants may be recommended. Portal thrombosis,[240] fatal mesenteric thrombosis,[59] thrombosis of the femoral artery,[237] thrombosis of the jugular vein,[78, 29] and

continued on next page

cerebral-vascular thrombosis[166] have occurred. Original claims that ACTH led to a shortened clotting time[238] have not been confirmed.[241]

Conversely a bleeding tendency may result from treatment. Forsham[222] lists a bleeding tendency as a contraindication to the use of ACTH or cortisone. Easy bruising,[214] purpura,[155] ecchymoses,[8] gastrointestinal hemorrhages (see below), hemorrhagic diathesis with scurvy,[212, 211] menorrhagia in 2.3% of female patients, one requiring laparotomy,[163] the release of heparin like substances,[242] unusual dicumarol sensitivity during therapy,[238] and a uniform fall in plasma fibrinogen[36, 37] are reported. However, some patients with purpura, with or without thrombocytopenia, have been reported to improve dramatically with ACTH or cortisone. (See Part I.)

X. UNDESIRABLE SEROLOGICAL EFFECTS

Undesirable serologial changes may mediate in part one of the most serious complications of therapy, intercurrent infection. Infection may begin during therapy or spread from a previously controlled focus. In either case its clinical manifestations of fever, pain, malaise, toxicity, rising sedimentation rate, or leukocytosis are suppressed or obscured so that one may not suspect the presence of infection until autopsy.[243, 244, 278] Pneumonia, tuberculosis and peritonitis are the chief offenders. An unsuspected pneumonia due to Friedlander's bacillus was discovered at autopsy in one patient.[245] Consolidation of 5 lobes is reported to have occurred without physical signs one hour before death.[244] Staphylococcal septicemia[61, 39] or purulent meningitis[246] may occur. Tuberculosis, especially miliary, has occurred incidental to therapy in at least 10 instances.[247, 248, 130] Known tuberculosis, even though stable for years, is probably a contraindication to therapy.[69, 240, 249, 250, 246, 250, 251, 257]

Incidental infections have occurred in 4-20%.[38, 68, 252, 253, 149] Animal experiments confirm the likelihood of this complication.[199, 200] The explanation does not seem to be in an impairment of antibody formation[83, 89, 254] but rather in an interference with the protective effects of antibodies. Phagocytic mechanisms are impaired[255] and fibroblastic restraint inhibited.[209] Prophylactic antibiotic therapy may not prevent the occurrence of fatal infections.[149, 245]

Preliminary reports suggest some infections appear to be exacerbated by therapy. North American blastomycosis,[256] nocardiosis,[246, 284] malaria,[18, 258] poliomyelitis in hamsters,[83, 279] virus pneumonia,[83] purulent arthritis in mice,[259] and bacterial infections, ringworm and vaccinia in the guinea pig[284] are made worse by ACTH or cortisone.

XI. UNDESIRABLE HEMOCYTOLOGIC EFFECTS

Undesirable hemocytologic effects include a leukocytosis as high as 25,000 and as frequent as 74% of one series.[103] This is not known to be harmful but it obscures the value of a leukocytosis as an index of infection. Although anemic patients may show an increase in red cell mass[233] with ACTH suppression of the underlying disorder, polycythemia has not been reported.[38, 103] In fact, depression of marrow function may result from therapy. ACTH causes serious atrophy of bone marrow in rats.[179] The ability of the marrow to recover from severe radiation damage in rats is impaired by cortisone.[285] ACTH may precipitate a crisis in a patient with sickle cell anemia.[258] Acute monocytic leukemia[38, 134] and some cases of acute myelogenous leukemia[195, 136] are said to be accelerated.[17]

XII. UNDESIRABLE GASTROINTESTINAL EFFECTS

Undesirable gastrointestinal effects include one of the most dangerous complications of therapy—peptic ulceration. Epigastric discomfort occurs in 5%.[38, 156] Silent perforation or hemorrhage are frequently fatal and may not be recognized until autopsy. There are at least 20 reports.[260, 261, 262, 263, 264, 265, 166, 17, 245, 283] This complication can be produced predictably in rats.[266, 199, 200] The mechanisms involved presumably include the known cortisone stimulation of gastric pepsin and hydrochloric acid, depression of lysozyme, protein catabolism with impaired fibroblastic defense reactions and obscuration of clinical signs of pain, fever, and toxicity. The relation to stress ulcers, Cushing's and Curling's ulcers is speculative.[267, 268, 269]

The failure of intestinal anastomoses,[160] bowel hemorrhage,[48] rectal abscess,[259] hypokalemic ileus,[174, 270] flatulence and epigastric distress from oral cortisone[271, 8] are other gastrointestinal complications.

XIII. UNDESIRABLE HEPATIC EFFECTS

The treatment of liver disease has been complicated by ascites,[213, 123] intra-abdominal hemorrhage, portal vein thrombosis and esophageal hemorrhage.[125]

XIV. UNDESIRABLE RENAL EFFECTS

ACTH and cortisone in patients with kidney disease causes an added renal work load with increased protein catabolism and release of potassium and urea. Two-thirds of patients with renal disease develop electroyte abnormalities—contrasted with only 17% in patients without renal lesions.[156] ACTH impairs tubular reabsorption of potassium[272, 273] leading to hypokalemia. When renal disease is more severe and urine volume is inadequate fatal hyperkalemia may ensue.[149, 150]

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Uremia is reported to result from therapy.[149, 165, 8] Hypertension is common during treatment in patients with renal disease. Acute glomerulonephritis has been reported to be made much worse by cortisone[75] and may appear with increased frequency.[76, 55] Cortisone potentiates various types of renal damage in rats.[274, 199, 200, 275]

XV. UNDESIRABLE MUSCULAR EFFECTS

Undesirable muscular effects probably due to protein catabolism include weakness which may be severe and persistent.[162, 38, 153, 155, 8] It may be especially disabling in patients with muscular disorders such as dystrophy, atrophy, dermatomyositis or cachexia.

XVI. UNDESIRABLE OSSEOUS EFFECTS

Osteoporosis, which is so prominent in Cushing's syndrome, may be expected to result from the protein catabolism and negative calcium balance if cortisone is given over several months. Eleven pathologic fractures of the spine, hip, and humerus associated with therapy have been reported.[153, 237, 155, 166, 156] An impaired ability to knit fractures has been shown in cortisone treated animals.[276]

Withdrawal arthritis is suggested as a term for the arthralgia which may occur for the first time upon stopping treatment. Joint effusion or X-ray changes of synovial thickening may occur.[277, 198] This process may play a role in the frequently seen violent relapse of rheumatoid arthritis after ACTH is stopped.[48, 184]

SUMMARY OF PART II

Table IV summarizes the ten most important undesirable effects of ACTH and cortisone. Their approximate incidence is based upon a total of 564 treated patients from seven reports. The dangers of these undesirable effects can be minimized if certain precautions are taken.

TABLE IV

Summary of Complications of Adreno-Cortical Hormone Therapy

Complication	*Incidence*	*Suggestion*
1. Intercurrent infection	4%	High index of suspicion and chemotherapy
2. Peptic ulcer with perforation or hemorrhage	1%	High index of suspicion
3. Diabetes	4%	Insulin *ad lib*
4. Hypertension	19%	Use cortisone instead of ACTH
5. Congestive failure	(if heart disease)	Vigorous diuresis

continued on next page

6. Psychosis	4%	Rule out low potassium
7. Epilepsy	2%	Dehydrate
8. Uremia	(if renal damage)	Rule out high potassium
9. Poor wound healing	20%	Testosterone?
10. Osteoporosis	4%	Testosterone?

The selection of patients for therapy must be made with an awareness of the special risks involved if there is any history of tuberculosis, peptic ulcer, diabetes, hypertension, congestive failure, mental abnormalities, epilepsy, uremia, bleeding tendency, osteoporosis or recent wounds.

Similarly the pre-treatment examination should ensure that none of these conditions are present—or if they are, that one is fully aware of the additional precautions necessary to follow the patient on therapy. Thus, preliminary routine tests should include a chest x-ray, serologic test for syphilis, postprandial blood sugar, urinalysis, and electrocardiogram. Others also recommend a glucose tolerance test, blood urea nitrogen, prothrombin time, serum cholesterol and basal metabolic rate. It is of value to have a pre-treatment absolute eosinophile count since if treatment fails to reduce the eosinophiles to less than half the initial value, one suspects the dosage schedule has been inadequate. Of course the converse does not follow.

During treatment it is urged that the patient's initial week be spent in a hospital to ensure that he receives a daily weight to follow fluid retention, a daily blood pressure to warn of hypertension and frequent postprandial urinalyses for sugar which can be checked by blood sugars and covered with insulin as necessary. The electrocardiogram may be repeated each week to be certain the oral supplement of potassium is adequate to prevent hypokalemia. The patient should be followed at frequent intervals with x-ray of the lungs to guard against intercurrent pneumonia or tuberculosis. The abdomen should be palpated for slight rigidity and tenderness that may indicate peritonitis. If the metabolic rate falls, the cholesterol rises, or the patient is not responding as expected, a trial of thyroid may be of value.

Most patients on therapy should receive a high protein, low salt diet with potassium chloride supplement, 3-6 Gms. a day if the urine volume exceeds one liter. Some have recommended the routine use of antibiotics, vitamins A and C, thyroid 30 mg. a day, and testosterone propionate (in males only) 25 mg. three times a week to minimize protein catabolism.

If diabetes develops it is well to use insulin freely to control hyperglycemia and protect the pancreas. If edema occurs, the use of mercurial diuretics will be helpful, but may also cause marked potassium diuresis which must be corrected. If the patient has an ulcer history and therapy is still indicated, a prophylactic anti-ulcer regimen would be reasonable. If any alarming symptoms develop or an intercurrent infection is suspected, one should stop treatment for two days in order to obtain a clearer picture.

Throughout treatment one must realize that the aim is to use the smallest necessary dose. Only the clinical course is an adequate measure of adequate dosage. If the dosage level or duration of treatment are unnecessarily excessive, the opportunities for undesirable complications are increased.

It is apparent that these remarkable new hormones should be used only if one keeps in mind their physiologic actions which include no curative properties, and have far reaching and frequently undesirable biological consequences.

BIBLIOGRAPHY

Due to the limitation of space the extensive bibliography of this paper has not been published in this Journal. The complete bibliography, however, is available on request.

... The Editor

BOOK REVIEWS

THE SPECIALTIES IN GENERAL PRACTICE, edited by Russell L. Cecil, M.D. W. B. Saunders Company, Phil., 1951. $14.50

This is a well conceived and executed book, edited by an old hand who has not lost his touch. It consists of a brief preface by the editor, a detailed table of contents, and 14 chapters, each discussing in considerable detail one of the surgical or medical specialties. The expressed purpose of these articles is to discuss the given specialty especially for the use of the general practitioner. In most cases, an attempt is made to discuss the commonly occurring problems of the specialty, and to distinguish between those conditions which the general man may cope with successfully, and those which he should refer for specialized examination or treatment. There is a small bibliography at the end of each chapter, and a complete index.

I will try to make a few comments about the individual chapters. Minor Surgery discusses preoperative care, a few congenital anomalies, injuries, including burns, infections, with a good discussion of hand infections, and a few other special procedures, such as paracentesis. Of special interest to the general man in the orthopedic section is an excellent discussion of low back pain. Fractures are well reviewed, with a wonderful chart entitled "Fracture Treatment Guide," giving, for each fracture, first aid, complications, anesthesia, reduction, immobilization, and convalescence. Urology includes several good diagnostic charts. Perhaps the finest section, in spite of its lowly subject matter, is that on diseases of the Anus, Rectum and Colon, by Dr. Charles A. Child. Written with great distinction, it includes a fine description of perianal endoscopy, a discussion of constipation which could well be read by all physicians from time to time, and a thorough review of all diseases of that region. The pediatric discussion is also excellent. Dr. Eley has selected a group of pertinent problems in this field, rather than attempting a comprehensive survey. These include infant nutritional requirements, immunization procedures, and a fine general review of convulsions in infancy and childhood. Ophthalmology includes a good review of the eyeground examination, and a useful list of eye medications. Of note in the nose and throat section is a fine description of the anatomy and physiology of those organs, with some sound advice about colds, sinuses, nose drops, headaches, and other daily problems of the general practitioner. Disease of the Larynx, Bronchi, and esophagus are ably discussed by Chevalier Jackson. Otology has a timely discussion of the modern treatment of otitis media, with a special plea against the inadequate use of the sulfa drugs, and the antibiotics. Dermatology and syphilology ably covers the common skin ailments, with many good black and white photographs. The last chapter, Psychiatry, is a quite condensed review of a large subject, touching only the highlights. Sections on interviewing, and the relationship between physician and patient seemed to present some worthwhile points.

It has been a pleasure to reveiw this book. It should serve as valuable quick reference for many of the daily problems confronting the practitioner and it should fulfill well the objectives for which it was written.

ROBERT W. DREW, M.D.

LIVING IN BALANCE by Frank S. Caprio, M.D. The Arundel Press, Inc., Wash., 1952. $3.75.

Dr. Caprio has written an interesting book—clear, lucid and in language simple and understandable. His descriptions of the neurotic vs. the normal, and how people develop neurotic traits, make fascinating and comprehensible reading for the lay public. Much of it is over-simplified, though this may be geared to lay understanding. I feel, however, that Dr. Caprio is mistaken in thinking that he can lay down sets of rules which presuppose that the person with neurotic traits can follow them to a good and happy life.

"Living in Balance" is excellent in its very clear presentation of emotional conflict in marital and sexual matters. I recommend especially Chapters XIII to XX to psychiatrically trained marriage counselors as a source of real help to those whose marriages, homes and families they are trying to save.

I would also recommend Chapter XXVI, "Balanced Living After Fifty." The simplicity with which this subject is handled makes it peculiarly adaptable to the layman.

Altogether, I think that Dr. Caprio's book has much to recommend it and should prove to be interesting and instructive reading to professional workers and laymen, alike.

GERTRUDE L. MULLER, M.D.

DYNAMIC PSYCHIATRY by Louis S. London, M.D. Vol. 1—Basic Principles; Vol. 2—Transvestism-Desire for Crippled Women. Corinthian Publications, Inc., N. Y., 1952.

This is a two-volume work, Volume I consisting of 95 pages, and Volume II of 126 pages. The title, "Dynamic Psychiatry," pertains to the contents only in the most tangential sort of way. Of the 95 pages of the first volume, 47 of them are devoted to "An evolution of psychotherapeutics from antiquity to the time of Freud." This so-called evolution consists essentially of a series of quotes and abstracts from recent works on the history of psychiatry, but could hardly be intended as a comprehensive review of either the evolution or the history of psychiatry. The author seldom goes to the original source for any of his statements, but quotes quotes of recent reviews extensively. From this so-called evolution the author proceeds into a chapter entitled, "The Meaning of the Dream," in which random quotations from the Bible and recent psycho-analytical works are liberally sprinkled, with no scientific evidence of the real meaning of the dream offered. A chapter on the psychology of the Libido completes the first volume. In this the author seems interested primarily in trying to impress the reader with the impossibility of the clinical psychiatrist understanding mental phenomena without also being a psycho-analyst. "The psychosexual pathology of the schizophrenic must be examined before we can determine the diagnosis and this can only be performed by psycho-analysis."

The second volume, with a sub-title "Transvestism—Desire for Crippled Women," consists of more history, a great share of which is devoted again to random quotes from ancient literature in which he seems to try to establish the fact that the Transvestism in general represents a latent homosexuality (as if in general this were not already accepted). The next 100 pages are devoted to 50 reproductions of a series of fantasies by a patient under analysis by the author, all of which consist of grotesque drawings of crippled women in various stages of men's dress or vice versa. Then follows twelve more pages entitled "Analysis of Case," which is essentially a series of quotes from the patient's associations, including his dreams. The author attempts to sum up the psychological dynamics of this complicated case in slightly less than two pages by establishing the, "latent homo-sexuality which is apparent in this patient as it is in all cases of Transvestism."

As in the case of this quotation, my appraisal of the book is that it tells nothing new to the advanced student of psychiatry and psycho-analysis, and it fails utterly to give a reasonable perspective to the newcomer. This very brief discussion of dreams and Libido, followed by an extremely brief discussion of a case of Transvestism gives approximately the same perspective of dynamic psychiatry that a description of the New York Subway System, accompanied by fifty different sketches of Grant's Tomb, would contribute to an adequate perspective of the City of New York as a whole.

C. H. CRONICK, M.D.

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U. S. DEFENSE BONDS

Certain improvements in the status of United States Defense Bonds, urged upon the Treasury Department for some time by his volunteer committee, have been announced by Chester R. Martin, Chairman of the Rhode Island Committee for the Savings Bonds Division. Believing these improvements are of interest to all who hold investments in this form of security, Martin has summarized them as follows:

Series E Bonds—Beginning May 1, 1952, they have an investment yield of 3% when held to maturity which is nine years, eight months. Previously, these bonds paid 2.9% when held to maturity in 10 years. Intermediate yields, when improved E Bonds are cashed before maturity, have been increased to a comparable degree, earnings beginning at six months instead of at one year after purchase. Yield in the extended maturity period of 10 years also is 3%. An improved $100 bond bought for $75 now pays $100 at 9⅔ years and $134.68 at 19⅔ years. Old E Bonds maturing before May 1, 1952, bear the previous extended maturity yield of 2.9%. Old E Bonds maturing after May 1, 1952, bear the new extended maturity yield of 3%.

Series F and G Bonds—These 12-year current income bonds have been discontinued as of May 1, 1952.

Series H Bonds — New current income face-value bonds mature in 9⅔ years and pay 3%; most provisions being parallel with Series E Bonds. Interest begins six months after purchase and bonds are redeemable at any time before maturity at face value. There is no extended maturity provision for H Bonds.

Series J and K Bonds—Replacements for the former F and G Bonds, having the same characteristics as their predecessors except J and K Bonds will pay 2.76% interest when held to their 12-year maturity. The F Bond paid 2.53% and the G Bond, 2.5%. Appreciable interim yield increases have been made in the new bonds.

All banks now are in possession of further details.

355 MD's TO BE INDUCTED

The Department of Defense has requested the Selective Service System to deliver to Armed Forces Induction Stations 355 doctors of medicine and 90 doctors of dentistry during the month of September.

The Armed Forces will assign 180 physicians to the Army and 175 to the Air Force.

All of the dentists will be assigned to the Air Force.

The September call for physicians and dentists brings to a total of 1,522 the number of physicians and to 650 the number of dentists requested since July, 1951.

Fiske Fund Prize Dissertation

1952

The Trustees of the Fiske Fund announce the following subject for the Prize Dissertation of 1952:

"The Present Status of Anti-Coagulant Therapy."

For the best dissertation on this subject worthy of a premium they offer the sum of two hundred dollars ($200.00). The dissertation will be particularly graded on the basis of original work by the author and his observation of patients. Each competitor for the premium is expected to conform with the following regulations:

To forward to the secretary of the Trustees on or before the second day of December, 1952, free of all expense, a copy of his dissertation with a motto thereon, and also accompanying it a sealed envelope bearing the same motto, inscribed on the outside, with his name and address within.

Previously to receiving the premium awarded, the author of the successful dissertation must transfer to the Trustees all his right, title and interest in and to the same, for the use, benefit, and behoof of the Fiske Fund. The successful author must agree to read his paper before the Rhode Island Medical Society at its annual meeting to be held in Providence in May, 1953.

Letters accompanying the unsuccessful dissertations will be destroyed unopened by the Trustees, and the dissertations may be procured by their respective authors if application be made therefor within three weeks.

The dissertations must be typewritten, double spaced on standard typewriter paper, and should not exceed 10,000 words. If the dissertation is illustrated, such illustrations will be published at the expense of the author.

John E. Farrell, SC.D.
SECRETARY to the TRUSTEES
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Albert H. Jackvony, M.D.
Louis E. Burns, M.D.
Earl F. Kelly, M.D.
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BOOK REVIEWS

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A TEXTBOOK OF CLINICAL NEUROLOGY by Israel S. Wechsler, MD., W. B. Saunders Company, Phil., 1952. 7th ed. $9.50.

This excellent text on Neurology was first written over 25 years ago and has now gone through seven editions. This, of itself, is proof of its value to the practicing physician and student. Its survival is not by chance but is written by a well-known neurologist and clinician who has drawn from his wide experience in a very large city with a wealth of neurological material.

The seventh edition is written with clear objectivity. The illustrations are well done. The section on examination and neurological signs is excellent. It also brings Psychiatry & Neurology closer by including Psychological diagnostic procedures. The section on the Neurosis is well done.

This volume is made easier to use for quick reference by the paragraph headings and important words or phrases in italics.

The classification and section on muscular atrophies is especially good. Other sections on particular subjects, such as, Neuro-anatomy, Aphasia, Basal Ganglia disease, etc. are to the point, succinct, clear and well done. Tumors of the C. N. S. are well handled, comprehensive and easily understood.

Treatment also is up to date and valuable new methods are discussed. Where knowledge is limited or conflicting views exist they are discussed with frankness. The brevity of the description of disease entities is as it should be in a text of this length and is without elaboration.

To balance this fine text, the last chapter on the INTRODUCTION to HISTORY of NEUROLOGY is inspiring to the student and gives just the right perspective. The index as usual is complete and references adequate.

In summary, it is hard to see how such a large and important subject could be handled any better in a text of 800 pages.

LAURENCE A. SENSEMAN, M.D.

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